

## General

### Guideline Title

Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline.

### Bibliographic Source(s)

Lutz S, Balboni T, Jones J, Lo S, Petit J, Rich SE, Wong R, Hahn C. Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. *Pract Radiat Oncol*. 2017 Jan-Feb;7(1):4-12. [39 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W, American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys*. 2011 Mar 15;79(4):965-76.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Recommendations

### Major Recommendations

The American College of Physicians (ACP) process for assigning strength of recommendation (Strong, Weak) and grading of quality of evidence (High-, Moderate-, and Low-Quality) is defined at the end of the "Major Recommendations" field.

Key Question (KQ) 1: What fractionation schemes have been shown to be effective for the treatment of pain and/or prevention of morbidity from peripheral bone metastases?

#### Guideline Statement

An updated review of high-quality data continues to show pain relief equivalency following a single 8 Gy fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions for patients with previously unirradiated painful bone metastases. Patients should be made aware that single-fraction (SF) radiation therapy (RT) is associated with a higher incidence of retreatment to the same painful site than is fractionated treatment. (High Quality Evidence, Strong Recommendation)

KQ 2: When is SF RT appropriate for the treatment of pain and/or prevention of morbidity from

uncomplicated bone metastasis involving the spine or other critical structures?

Guideline Statement

A single 8 Gy fraction provides noninferior pain relief compared with a more prolonged RT course in painful spinal sites and may therefore be particularly convenient and sensible for patients with limited life expectancy. (High Quality Evidence, Strong Recommendation)

KQ 3: Are there long-term side-effect risks that should limit the use of SF therapy?

Guideline Statement

There continues to be no suggestion from available high-quality data that SF therapy produces unacceptable rates of long-term side effects that might limit its use for patients with painful bone metastases. The evidence regarding an association between higher risk for pathologic fracture after SF therapy versus fractionated therapy remains equivocal. (High Quality Evidence, Strong Recommendation)

KQ 4: When should patients receive retreatment with radiation to peripheral bone metastases?

Guideline Statement

Patients with persistent or recurrent pain more than 1 month following EBRT for symptomatic, peripheral bone metastases should be considered for retreatment while adhering to normal tissue dosing constraints described in the available literature. (High Quality Evidence, Strong Recommendation)

KQ 5: When should patients receive retreatment with radiation to spine lesions causing recurrent pain?

Guideline Statement

Patients with recurrent spine pain more than 1 month after initial treatment should be considered for EBRT retreatment while adhering to normal tissue dosing constraints described in the available literature. (High Quality Evidence, Strong Recommendation)

KQ 6: What promise does highly conformal RT hold for the primary treatment of painful bone metastasis?

Guideline Statement

Advanced RT techniques such as SBRT as the primary treatment for painful spine bone lesions or for spinal cord compression should be considered in the setting of a clinical trial or with data collected in a registry given that insufficient data are available to routinely support this treatment currently. (Moderate Quality Evidence, Strong Recommendation)

KQ 7: When should highly conformal RT be considered for retreatment of spine lesions causing recurrent pain?

Guideline Statement

Advanced radiation techniques such as SBRT retreatment for recurrent pain in spine bone lesions may be feasible, effective, and safe, but the panel recommends that this approach should be limited to clinical trial participation or on a registry given limited data supporting routine use. (Moderate Quality Evidence, Strong Recommendation)

KQ 8: Does the use of surgery, radionuclides, bisphosphonates, or kyphoplasty/vertebroplasty obviate the need for palliative RT for painful bone metastasis?

Guideline Statement

The panel reiterates that the use of surgery, radionuclides, bisphosphonates, or kyphoplasty/vertebroplasty does not obviate the need for EBRT for patients with painful bone

metastases, although 1 recent trial has suggested the potential for similar, albeit less rapid, bone pain relief in prostate cancer patients following an infusion of ibandronate when compared with a single fraction of EBRT. (Moderate Quality Evidence, Strong Recommendation).

## Definitions

### Grading of Quality of Evidence

#### *High-Quality Evidence*

Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

#### *Moderate-Quality Evidence*

Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

#### *Low-Quality Evidence*

Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose–response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

### Grading of Guideline Recommendations

#### *Strong Recommendation*

Evidence suggests that the benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus.

#### *Weak Recommendation*

Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or non-uniform consensus.

## Clinical Algorithm(s)

None provided

## Scope

## Disease/Condition(s)

Bone metastases

## Guideline Category

Assessment of Therapeutic Effectiveness

Management

Treatment

## Clinical Specialty

Nuclear Medicine

Oncology

Radiation Oncology

Radiology

Surgery

## Intended Users

Physicians

## Guideline Objective(s)

- To provide an update of the Bone Metastases Guideline published in 2011 based on evidence complemented by expert opinion
- To consider new high-quality evidence for the 8 key questions (KQs) from the original guideline

## Target Population

Patients with bone metastases

## Interventions and Practices Considered

1. External beam radiotherapy (EBRT)
2. Single- versus multiple-fraction radiation schedules
3. Repeat radiotherapy
4. Stereotactic body radiotherapy (considered but not recommended as primary treatment outside of clinical trials)

## Major Outcomes Considered

- Pain relief
- Overall survival
- Progression-free survival
- Recurrence
- Toxicity (acute and late)
- Quality of life
- Long-term side-effects

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

## Description of Methods Used to Collect/Select the Evidence

### Literature Review

A systematic review was initially conducted by the American Society for Radiation Oncology (ASTRO) staff of English-language studies in PubMed published between the last date searched in the original guideline, December 22, 2009, and June 17, 2014. Following approval of the update proposal, the review was extended through January 7, 2015. Terms common to all searches included: bone metastasis, bone metastases, radiation, and radiotherapy. Additional specific terms were incorporated for each Key Question (KQ) (see Appendix A in the original guideline document for literature search strategies). The outcomes of interest were overall and progression-free survival, recurrence, toxicity, and quality of life.

In total, 414 references meeting the inclusion criteria were retrieved by the PubMed searches and reviewed first by ASTRO staff and then by the whole panel. The inclusion criteria were: age  $\geq 18$  years; bone metastases that were previously unirradiated or causing recurrent pain after radiation therapy; and treatment with external beam RT (EBRT), intensity modulated RT, or stereotactic body RT (SBRT) with or without bisphosphonates, radiopharmaceuticals, kyphoplasty, or vertebroplasty. The exclusion criteria were: nonhuman, dosimetric-only, case report, and conference abstract. The results were further refined to include only randomized controlled trials (RCTs), meta-analyses, or prospective studies.

## Number of Source Documents

Ultimately, 56 studies were included and abstracted into evidence tables. One additional article representing significant new data for Key Question 8 was included in September 2015.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

### Grading of Quality of Evidence

#### High-Quality Evidence

Evidence is considered high quality when it is obtained from 1 or more well-designed and well-executed randomized controlled trials (RCTs) that yield consistent and directly applicable results. This also means that further research is very unlikely to change confidence in the estimate of effect.

#### Moderate-Quality Evidence

Evidence is considered moderate quality when it is obtained from RCTs with important limitations—for example, biased assessment of the treatment effect, large loss to follow-up, lack of blinding, unexplained heterogeneity (even if it is generated from rigorous RCTs), indirect evidence originating from similar (but not identical) populations of interest, and RCTs with a very small number of participants or observed events. In addition, evidence from well-designed controlled trials without randomization, well-designed cohort or case-control analytic studies, and multiple time series with or without intervention are in this

category. Moderate-quality evidence also means that further research will probably have an important effect on confidence in the estimate of effect and may change the estimate.

#### Low-Quality Evidence

Evidence obtained from observational studies would typically be rated as low quality because of the risk for bias. Low-quality evidence means that further research is very likely to have an important effect on confidence in the estimate of effect and will probably change the estimate. However, the quality of evidence may be rated as moderate or even high, depending on circumstances under which evidence is obtained from observational studies. Factors that may contribute to upgrading the quality of evidence include a large magnitude of the observed effect, a dose-response association, or the presence of an observed effect when all plausible confounders would decrease the observed effect.

## Methods Used to Analyze the Evidence

### Review of Published Meta-Analyses

### Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

All of the included studies were abstracted into evidence tables. The strength of the recommendation and supporting evidence were rated using the American College of Physicians process (see the "Rating Scheme for the Strength of the Evidence" and "Rating Scheme for the Strength of the Recommendations" fields). The chair initially assigned the ratings, which the panel later approved.

## Methods Used to Formulate the Recommendations

### Expert Consensus (Delphi)

## Description of Methods Used to Formulate the Recommendations

In May 2014, the guidelines subcommittee convened a work group to review available evidence and recommend whether the bone metastases guideline should be withdrawn, updated, or left intact. The group comprised 1 co-lead of the original guideline, 3 topic experts (2 not involved in the original guideline), and 4 guidelines subcommittee members. After review of new literature, the work group recommended an update of all Key Questions (KQs) from the original guideline and the proposal was approved by the American Society for Radiation Oncology (ASTRO) Board of Directors in November 2014. The update panel was identical to the work group. Through calls and e-mails, the panel formulated recommendation statements and narratives based on the literature review.

### Grading of Evidence and Recommendations and Consensus Methodology

The recommendation statements (see the "Major Recommendations" field) were developed based on high-quality evidence in accordance with Institute of Medicine standards. Panel consensus was evaluated in 2 rounds through a modified Delphi approach. In an online survey, panelists rated agreement with each recommendation on a 5-point Likert scale, from strongly disagree to strongly agree. A prespecified threshold of  $\geq 75\%$  "agree" or "strongly agree" responses indicated consensus. Following the first round, the recommendations for KQs 4 and 5, which cover reirradiation, were updated to emphasize the need for adherence to normal tissue constraints. The recommendations for KQs 6 and 7, addressing the role of highly conformal radiation therapy, initially failed to reach consensus and were revised to clarify the level of current evidence and the settings in which advanced technologies should be used. These 4 recommendations were re-rated and the results replaced those from the first round.

The strength of the recommendation and supporting evidence were rated using the American College of Physicians process (see the "Rating Scheme for the Strength of the Evidence" and the "Rating Scheme for the Strength of the Recommendations" fields). A strong recommendation indicated "benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus." A weak recommendation showed "benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or nonuniform consensus." The chair initially assigned the ratings, which the panel later approved.

## Rating Scheme for the Strength of the Recommendations

### Grading of Guideline Recommendations

#### Strong Recommendation

Evidence suggests that the benefit of the intervention outweighs the risk, or vice versa, and the panel has reached uniform consensus.

#### Weak Recommendation

Evidence suggests that the benefit of the intervention equals the risk, or vice versa, and the panel has reached uniform or non-uniform consensus.

## Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

## Method of Guideline Validation

### External Peer Review

### Internal Peer Review

## Description of Method of Guideline Validation

The draft manuscript was reviewed by 5 expert reviewers (see Acknowledgments in the original guideline document) and American Society for Radiation Oncology (ASTRO) legal counsel. The update was posted online for public comment December 2015 through January 2016. The final document was approved by the Board of Directors in April 2016.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

## Potential Benefits

Radiation therapy (RT) provides successful palliation of painful bone metastases that is time-efficient and associated with very few side effects.

Refer to the original guideline document for a discussion of evidence of benefits for specific statements.

## Potential Harms

- Single-fraction radiation therapy (SFRT) is associated with a higher incidence of retreatment to the same painful site than is fractionated treatment.
- Stereotactic body radiation therapy (SBRT) use for patients who present with spinal cord compression should be considered only with great caution given the absence of a physical separation between the target and adjacent normal critical structures.

Refer to the original guideline document for a discussion of evidence of potential harms for specific statements, including discussions of acute and late toxicities of radiation therapy.

# Qualifying Statements

## Qualifying Statements

- American Society for Radiation Oncology (ASTRO) guidelines present scientific, health, and safety information and may reflect scientific or medical opinion. They are available to ASTRO members and the public for educational and informational purposes only.
- Adherence to this guideline will not ensure successful treatment in every situation. This guideline should not be deemed inclusive of all proper methods of care or exclusive of other methods reasonably directed to obtaining the same results. The physician must make the ultimate judgment regarding any specific therapy in light of all circumstances presented by the patient. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. This guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials.
- This guideline was prepared on the basis of information available at the time the panel was conducting its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for ASTRO to revisit and update the guideline.

# Implementation of the Guideline

## Description of Implementation Strategy

An implementation strategy was not provided.

## Implementation Tools

### Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.



# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

End of Life Care

Living with Illness

## IOM Domain

Effectiveness

Safety

## Identifying Information and Availability

### Bibliographic Source(s)

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### Adaptation

Not applicable: The guideline was not adapted from another source.

### Date Released

2017 Jan-Feb

### Guideline Developer(s)

American Society for Radiation Oncology - Professional Association

### Source(s) of Funding

American Society for Radiation Oncology

### Guideline Committee

American Society for Radiation Oncology (ASTRO) Guidelines Subcommittee

Palliative Radiation Therapy for Bone Metastases Guideline Update Panel

### Composition of Group That Authored the Guideline

*Panel Members:* Stephen Lutz, MD, Department of Radiation Oncology, Eastern Woods Radiation Oncology, Findlay, Ohio; Tracy Balboni, MD, MPH, Department of Radiation Oncology, and Department of Psychosocial Oncology and Palliative Care, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, Massachusetts; Joshua Jones, MD, Department of Radiation Oncology, University of Pennsylvania Health System, Philadelphia, Pennsylvania; Simon Lo, MB, ChB, Department of Radiation Oncology, University of Washington School of Medicine, Seattle, Washington; Joshua Petit, MD, Department of Radiation Oncology, University of Colorado Health, Fort Collins, Colorado; Shayna E. Rich, MD, PhD, Hospice and Palliative Medicine, Mayo Clinic College of Medicine, Jacksonville, Florida; Rebecca Wong, MB, ChB, Department of Radiation Oncology, Princess Margaret Hospital, Toronto, Ontario, Canada; Carol Hahn, MD, Department of Radiation Oncology, Duke University Medical Center, Durham, North Carolina

## Financial Disclosures/Conflicts of Interest

Before initiating work on this guideline, all panelists completed disclosure statements and pertinent disclosures are published within this report. Where potential conflicts are detected, remedial measures to address them are taken and noted here. Tracy Balboni received research funding from Templeton Foundation and leads ongoing bone metastases study. Simon Lo participated in international oligometastases consortium partially funded by Elekta and received honoraria and travel expenses from Accuray and Varian. These disclosures were shared with the panel. The panel and guideline subcommittee chair reviewed these relationships and determined that the disclosure here is sufficient to manage potential conflicts.

## Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, Howell D, Konski A, Kachnic L, Lo S, Sahgal A, Silverman L, von Gunten C, Mendel E, Vassil A, Bruner DW, Hartsell W, American Society for Radiation Oncology (ASTRO). Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys*. 2011 Mar 15;79(4):965-76.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Available from the [Practical Radiation Oncology Web site](#) .

## Availability of Companion Documents

The following is available:

Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. Appendices A & B. Available from the [Practical Radiation Oncology Web site](#) .

## Patient Resources

The following is available:

Radiation therapy for palliative care. Patient brochure. American Society for Radiation Oncology; 2015. 2 p. Available from the [RTAnswers Web site](#) .

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## NGC Status

This NGC summary was completed by ECRI Institute on April 20, 2012. The information was verified by the guideline developer on May 29, 2012. This summary was updated by ECRI Institute on April 7, 2017. The updated information was verified by the guideline developer on May 3, 2017.

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